

•Original Article•

Relationship between traditional Chinese medicine syndrome differentiation and imaging characterization to the radiosensitivity of nasopharyngeal carcinoma

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[Abstract] Background and Objective: Traditional Chinese medicine (TCM) is a well established and time-honored practice in China, employing syndrome differentiation as a basis for the treatment of disease. According to different TCM syndrome typing findings, combining modern medical methods with TCM approaches can improve the quality of life and comprehensive effect on patients with nasopharyngeal carcinoma (NPC). This study investigated the relationship between TCM syndrome typing and imaging characterization to radiosensitivity as to provide objective evidence for the integration of Chinese and modern medical approaches in the treatment of NPC. **Methods:** Prior to treatment, TCM syndrome typing, computed tomography (CT) and magnetic resonance imaging (MRI) were performed on 147 patients pathologically classified with NPC. The status of tumor remission was radiologically evaluated at accumulated doses of 20 Gy, 40 Gy and 60 Gy, and at 3 months after completion of radiotherapy. Statistical results were analyzed by the Friedman and K-W test procedures. **Results:** Prior to treatment, TCM syndrome typing of NPC included Lung Heat, Blood Stasis, Phlegm Congealment and Blood Stasis-Phlegm Congealment. Lung Heat typing accounted for the highest proportion at 34.7% (51/147), followed by Phlegm Congealment at 32.7% (48/147), Blood Stasis at 17.0% (25/147) and Blood Stasis-Phlegm Congealment at 15.7% (23/147). Radiological imaging demonstrated a higher incidence of cervical lymph node metastases in Phlegm Congealment and Blood Stasis-Phlegm Congealment types ($P < 0.05$), while Blood Stasis and Blood Stasis-Phlegm Congealment types were more prone to skull base invasion ($P < 0.05$). Residual tumor size was larger in Blood Stasis and Blood Stasis-Phlegm Congealment types than in Lung Heat and Phlegm Congealment types after 3 months of treatment ($P < 0.05$). **Conclusions:** Different radiological manifestations were observed in TCM syndrome typed NPC patients, with lesser radiosensitivity demonstrated in the Blood Stasis and the Blood Stasis-Phlegm Congealment types relative to the Lung Heat and Phlegm Congealment types.

Key words: Nasopharyngeal neoplasm, traditional Chinese medicine syndrome typing, radiological image, radiosensitivity

Nasopharyngeal carcinoma (NPC) is among the most commonly classified carcinomas of southern China, accounting for 80% of the global case load^[1]. At present,

ionizing radiation (IR) leading comprehensive therapy is the main treatment for NPC. Although most NPC patients achieve a good outcome from conventional radiotherapy, local relapse and distant metastasis with radiation resistance is very common.

For a great time there have been clinical studies on the biological behavior of NPC, in which different typing, including the clinical syndrome typing of TCM, have been suggested. Xie *et al.*^[2] classified advanced NPC into the ascending, descending and mixed types according to the

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course of natural development, whereas He *et al.*^[3] classified advanced NPC into the metastasis, invading, and mixed types according to the characteristics of metastasis and recurrence. Based on the radiotherapeutic outcomes of 1 302 NPC cases^[4] combined with cases of post-radiotherapeutic long-term, tumor-free survival^[5,6] and long-term, tumor-accompanied survival after low-dose radiotherapy^[7,8], we have summarized four types of NPC biology from the viewpoint of radiotherapy: radio-sensitive with low metastasis-prone, radio-sensitive with high metastasis-prone, radio-resistant with low metastasis-prone and radio-resistant with high metastasis-prone^[9].

Clearly, for radio-sensitive NPC, present radical radiotherapy (70–76 Gy) is an unacceptable over-dose, in which long-term damage of normal tissue is increased and the quality of life is affected. In addition, when chemotherapy is administered to low metastasis-prone patients, patients may suffer the unnecessary pain of chemotherapy. Finally, radio-resistant, high metastasis-prone NPC patients should receive an effective therapeutic regimen in the earlier stages of cancer development. Clinical studies have provided evidence for the standardized treatment of NPC. At present, strategies based on the anatomy of tumor invasion are being employed^[10,11]. In early stage cases, radiotherapy (T1–2N0–1M0) is advised. In moderate stage cases, radiotherapy alone (T3N0–1M0) and concomitant radio-chemotherapy (T1–3N2M0) is advised. In advanced stage cases, concomitant radio-chemotherapy (T4N0–3M0, TanyNanyM1) is advised.

The 5-year overall survival rate has risen dramatically in the past fifty years, reaching a plateau of 60% from 19%^[12–16]. Despite the common consent of good therapeutic effect of three-dimensional conformal radiotherapy for the treatment of NPC, the incidence of long-term radiation injury is high, with toxicity and side effects including loss of hearing, skin erythema, subcutaneous fibration, cerebral and neural injury. These aforementioned side effects are painful and potentially complicate the therapeutic regimen. Since individual tumors exhibit different biological behavior, specific radiotherapy for NPC, based on their biological behavior, is the ultimate goal of treatment.

The practice of TCM is the quintessence of Chinese culture. TCM is characterized by syndrome differentiation, whereby NPC patients are classified into different syndrome types and treated with approaches in Chinese medicine in an effort to lessen toxicity and side effects, improve the quality of life and raise the comprehensive curative effect of NPC treatment. Commonly, we make TCM syndrome differentiation by collecting clinical information through observing, listening, smelling, palpation and inquiry, foregoing modern imaging techniques and consideration of post-radiotherapeutic reaction. Thus, we made a preliminary

study on the relationship between TCM syndrome typing and imaging characterization to the radiosensitivity of NPC in an effort provide support for the individualized treatment of NPC by integrative traditional Chinese-modern medicine.

Patients and Methods

Patients

A total of 196 patients with pathologically confirmed NPC were enrolled in Sun Yat-sen University Cancer Center between December 2006 and December 2009. TCM syndrome differentiation, CT and MRI were performed prior to treatment. The status of tumor remission was radiologically evaluated at the accumulated radiotherapeutic doses of 20 Gy, 40 Gy and 60 Gy and at 3 months after the completion of therapy. Intact clinical data of 147 cases were collected, including the TCM syndrome typing, completion of radiotherapy, imaging data and curative effect evaluation. There were 109 male patients and 38 female patients, aged 9 to 74 years, with a mean age of 44.4 years and a median age of 44. Pre-treatment examination included CT and MRI; post-treatment evaluation included CT only. Pathologically, 133 patients were diagnosed with non-keratinizing undifferentiated carcinoma, 13 patients with non-keratinizing differentiated carcinoma and 1 patient with keratinizing squamous cell carcinoma. The Chinese 2008 staging system of NPC was adapted for clinical staging.

Methods

TCM syndrome differentiation

According to the Cancer Therapeutics of Integrative Chinese-Western Medicine (Zhong xi yi lin chuang zhong liu xue)^[17] and Practical Radiotherapy for Nasopharyngeal Carcinoma^[3], the syndrome types were identified as follows: (1) Lung Heat type: symptoms include blood-stained snivel and/or nasal obstruction, tinnitus and obstructive feeling in the ear; possible symptoms include dry mouth, red tip and margin of the tongue with thin white/yellowish coating, slippery or rapid pulse without headache and physical presence of neck lump(s). (2) Blood Stasis type: symptoms include headache and/or numbness of the face and diplopia; possible symptoms include blood-stained snivel, tinnitus, deafness, deviation of the mouth and eye, crooked tongue, nasal obstruction, dark tongue or tongue with ecchymosis, thin coating, unsmooth/knotted/intermittent pulse without physical presence of neck lump(s). (3) Phlegm Congealment type: symptoms include physical presence of a neck lump (s); possible symptoms of obstructive feeling in the ear, tinnitus, deafness, chest distention, bad appetite, pale red tongue with greasy/slippery white coating, thready and

slippery pulse without headache. (4) Blood Stasis-Phlegm Congealment type: symptoms include headache, neck lump (s) and those of Blood Stasis type and Phlegm Congealment type. (5) Qi-blood Deficiency type: Symptoms include a grayish and lusterless complexion, emaciation, dizziness, shortness of breath; possible symptoms of bad appetite, neck lump (s), deviation of mouth and eye, headache, numbness of face, pale tongue, and weak pulse. In an effort to minimize diagnostic subjectivity, syndrome differentiation was performed by more than 2 registered TCM doctors according to regimental standards. The sole Qi-blood deficiency typed patient did not complete the post-treatment imaging evaluation at three months after treatment and was removed from the study.

Computed tomography examinations

CT scans were performed on a spiral CT scanner (SIEMENS SOMATOM PLUS 4). Scan parameters were as follows: tube tension 120 kV, tube current 159 mA, effective slice thickness 3 mm, intersection gap 3 mm, pitch 1.0. Scanning range: from 2 cm superior to the frontal sinus to 2 cm inferior to the clavicle, including the skull base, nasopharynx and neck. Iopamidol (300 mgI/L, Bracco Sine Pharmaceutical Corp. Ltd, Shanghai), dosage 80–100 mL, was injected as an intravenous bolus at a rate of 2–3 mL/s. Imaging was initiated 45 s after the start of contrast material injection. CT scans at the accumulative doses of 20 Gy and 60 Gy were performed without contrast.

Magnetic resonance imaging

MR imaging was performed on a 1.5-Tesla unit (Signa CV/i 1.5 T, GE Medical Systems) using a head and neck coil. For all patients, standard T1-weighted spin echo sequences (T1 SE) in axial, sagittal and coronal planes, and T2-weighted turbo spin echo sequences (T2 TSE) in axial plan were obtained. Scan parameters are as follows: T1-weighted: TR/TE/flip 431 ms/13 ms/90°, FOV 22 cm, matrix 320 × 224, effective slice thickness 5 mm, intersection gap 1 mm, total 32 slices; T2-weighted: TR/TE/flip 4464 ms/120 ms/90°, FOV 230 mm × 230 mm, matrix 320 × 224, effective slice thickness 5 mm, intersection gap 1 mm, total 32 slices. Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA, Consun Pharmaceutical Group, Guangzhou), dosage 0.1 mmol/kg, was intravenously injected for contrast enhancement. T1-weighting with contrast imaging was initiated after the start of contrast material injection.

Imaging analysis

Imaging interpretation was performed by more than two senior radiologists through the workstation.

Radiotherapy planning and evaluating standards for tumor remission and radiosensitivity

For the radiation treatment planned through CT-SIM, the

definition of the target volume was as follows: the gross tumor volume (GTV) refers to the total volume of tumor detectable by diagnostic procedures. Clinical target volume (CTV)₆₀ = GTV + 5 mm + all the nasopharyngeal walls. CTV_{50–54} = GTV + 10 mm + posterior third of the nasal cavity + posterior third of the maxillary sinus + frontal third of sphenoid sinus + posterior ethmoid sinus + parapharyngeal space + area of carotid sheath + retropharyngeal space + internal and external pterygoid muscle. Generally, the GTV dose was 70 Gy, 60 Gy for CTV₆₀, and 50–54 Gy for CTV_{50–54}. The fractionation dose was 2 Gy/fraction (once a day, 5 times a week). Patients were examined by CT when accumulated doses reached 20 Gy, 40 Gy, or 60 Gy and at 3 months post-treatment. Pre- and post-treatment CT was performed under identical conditions relative to body posture and scanning parameters. When CT demonstrated complete tumor remission at the accumulated dose of 20 Gy, total dose was reduced to 60–66 Gy. When CT demonstrated residual tumor growth at the accumulated dose of 60 Gy, total dose was increased to 78 Gy. Tumor remission was evaluated as presented in Table 1; complete remission (CR), major partial remission (PR+), partial remission (PR), minor partial remission (PR-) and stable disease (SD), with the standard of radiosensitivity were defined as follows: High radiosensitivity type, CR at 20 Gy or PR+ at 20 Gy and CR at 40 Gy; moderate radiosensitivity type, under PR+ at 20 Gy but CR at 40 Gy or PR+ at 40 Gy and CR at 60 Gy; low radiosensitivity type, under PR+ at 40 Gy but CR at 60 Gy or PR+ at 60 Gy and CR at 3 months post-therapy; radio-resistant type, with tumor residual at 60 Gy and no CR at 3 months after completion of radiotherapy. CT of patients assigned different radiosensitivity types of NPC is presented in Figures 1–4.

Statistical analyses

Data was analyzed by SPSS11.5, a nonparametric test for data of non-normal distribution (Friedman test for related samples and K-W test for individual samples). Statistical significance was designated at $P < 0.05$.

Results

TCM syndrome typing

Lung Heat type accounted for the highest proportion at 34.7%, with Phlegm Congealment type at 32.7%, Blood Stasis type at 17.0%, and Blood Stasis-Phlegm Congealment type at 15.6% (Figure 5). The relationship between TCM syndrome typing and the characteristics of clinical manifestation and staging is shown in Table 2.

Table 1 Standardized clinical evaluation with computer tomography

Response evaluation criteria	Nasopharynx		Neck lymph nodes	
	Structure	Measurable tumor volume	Measurable tumor volume	Number of lymph nodes
CR	Nasopharyngeal lesions with complete remission	0	0	0
PR+	Eustachian orifice, pharyngeal recess returned to normal	Reduction $\geq 75\%$	100% > Reduction > 75%	Reduction > 75%
PR	Eustachian orifice returned to normal, pharyngeal recess remain filled	75% > Reduction > 50%	75% > Reduction > 50%	Reduction > 50%
PR-	Eustachian orifice, pharyngeal recess, structure unclear	50% > Reduction > 25%	50% > Reduction > 25%	Reduction > 25%
SD	Nasopharynx structure relatively unchanged from pre-treatment	Reduction < 25%	Stable, Reduction < 25%	Stable

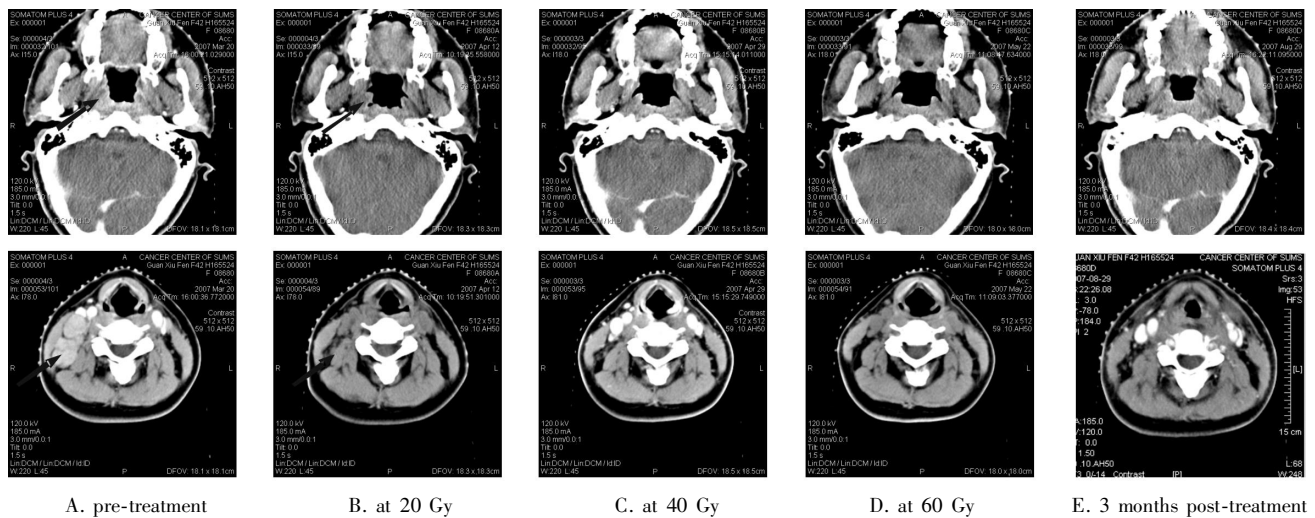


Figure 1 Computed tomography (CT) images of a very radiation-sensitive patient

Female, aged 42, Blood Stasis Phlegm typed. Radiological evaluation of the nasopharynx (top) and cervical lymph node (bottom) prior to (A) and at the accumulated radiotherapeutic doses of 20 Gy (B), 40 Gy (C) and 60 Gy (D) and at 3 months after completion of therapy (E). Complete remission of nasopharyngeal and cervical lymph node neoplastic growth is demonstrated upon clinical evaluation at 20 Gy.

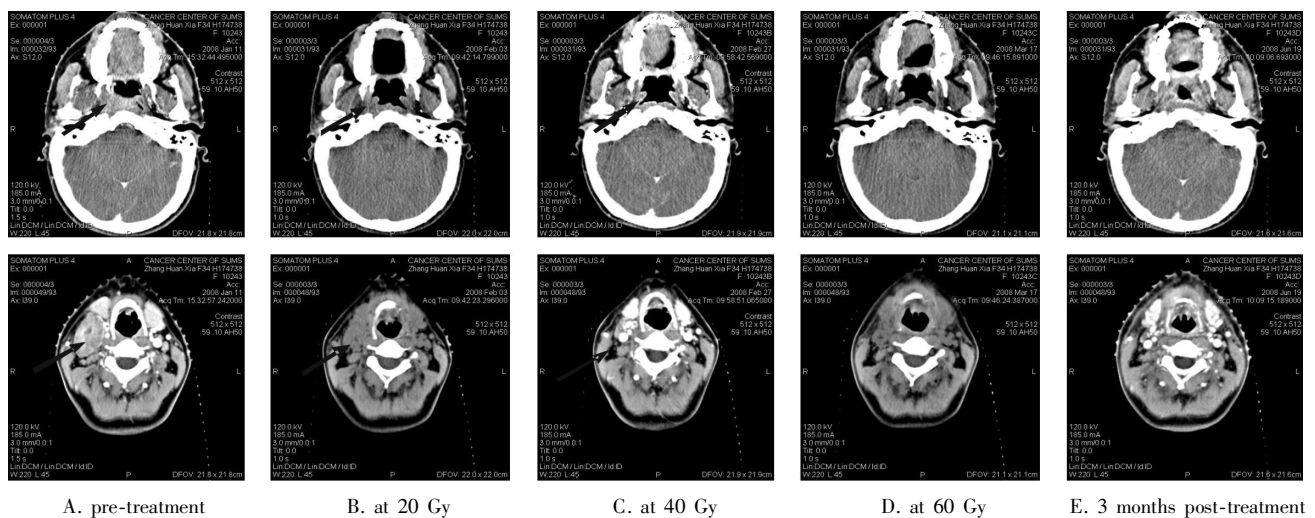


Figure 2 CT images of a moderately radiation-sensitive patient

Female, aged 34, Phlegm Congealment typed. Radiological evaluation of the nasopharynx (top) and cervical lymph node (bottom) prior to (A) and at the accumulated radiotherapeutic doses of 20 Gy (B), 40 Gy (C) and 60 Gy (D) and at 3 months after completion of therapy (E). Residual tumor growth is demonstrated upon clinical evaluation at 20 Gy with complete remission of neoplastic growth upon clinical evaluation at 40 Gy.

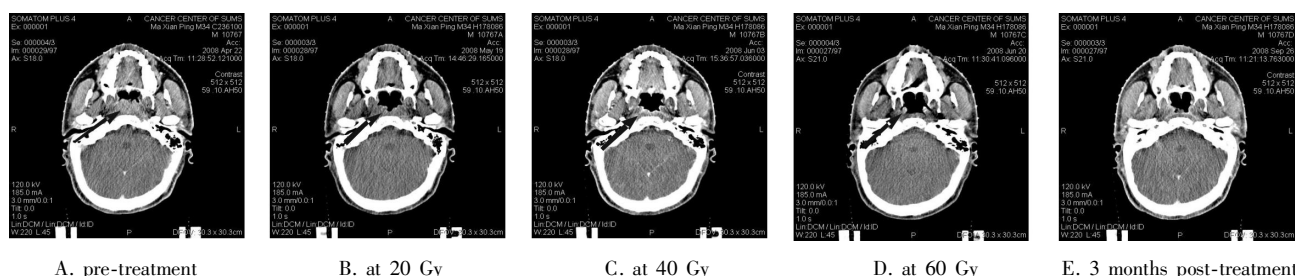


Figure 3 CT images of a poorly radiation-sensitive patient

Male, aged 34, Lung Heat typed. Radiological evaluation of the nasopharynx prior to (A) and at the accumulated radiotherapeutic doses of 20 Gy (B), 40 Gy (C) and 60 Gy (D) and at 3 months after completion of therapy (E). Residual tumor growth is demonstrated upon clinical evaluation at 20 Gy and 40 Gy with complete remission of neoplastic growth upon clinical evaluation at 60 Gy.

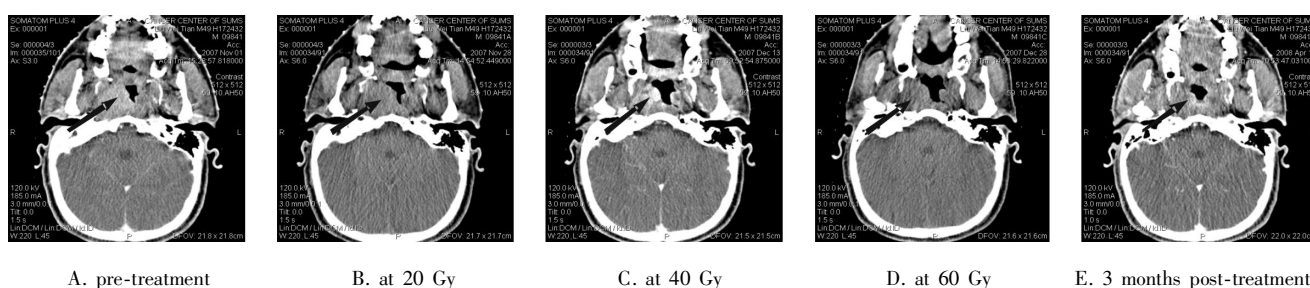


Figure 4 CT images of a radiation-insensitive patient

Male, aged 49, Blood Stasis-Phlegm Congealment typed. Radiological evaluation of the nasopharynx prior to (A) and at the accumulated radiotherapeutic doses of 20 Gy (B), 40 Gy (C) and 60 Gy (D) and at 3 months after completion of therapy (E). Residual tumor remains throughout the therapeutic regimen and after the treatment is concluded.

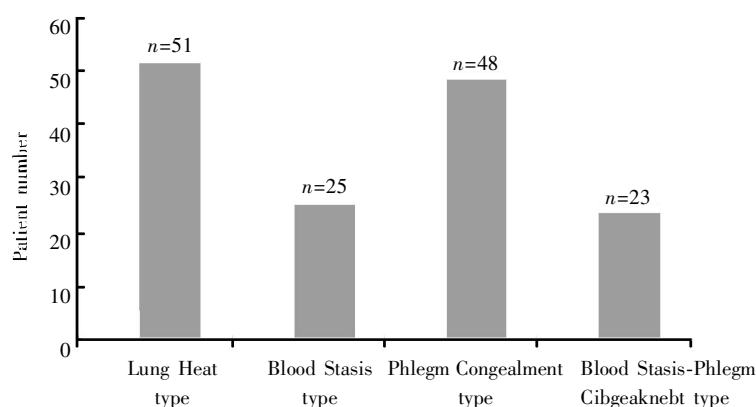


Figure 5 Traditional Chinese medicine (TCM) syndrome types of nasopharyngeal carcinoma
A total of 147 patients were classified into 4 groups according to their TCM syndrome types.

Relationship between TCM syndrome typing and imaging characterization

Regional NPC tumor ($\chi^2 = 1.59$, $P > 0.05$) and parapharyngeal space invasion ($\chi^2 = 3.64$, $P > 0.05$) had no significant association with different syndrome types of TCM, but cervical lymph node enlargement ($\chi^2 = 34.34$, $P <$

0.05) and destruction of bone in the skull base ($\chi^2 = 4.55$, $P < 0.05$) did correlate with different syndrome types. Phlegm Congealment type and Blood Stasis-Phlegm Congealment type were more likely to suffer from nodal metastasis, while Blood Stasis type and Blood Stasis-Phlegm Congealment type had a higher risk of destruction of bone in the skull base (Table 3).

Table 2 Clinical characterization of patients with nasopharyngeal carcinoma

Characteristic	Lung Heat type case (%)	Blood Stasis type case (%)	Phlegm Congealment type case (%)	Blood Stasis-Phlegm Congealment type case (%)
Total cases	51 (34.7)	25 (17.0)	48 (32.7)	23 (15.6)
Age (years)				
< 44	22 (15.0)	15 (10.2)	21 (14.3)	9 (6.1)
≥ 44	29 (19.7)	10 (6.8)	27 (18.4)	14 (9.5)
Gender				
Male	37 (25.2)	22 (15.0)	31 (21.1)	19 (12.9)
Female	14 (9.5)	3 (2.0)	17 (11.6)	4 (2.7)
T stage				
T1	7 (4.8)	0 (0)	6 (4.1)	0 (0)
T2	15 (10.2)	0 (0)	15 (10.2)	1 (0.7)
T3	26 (17.7)	7 (4.8)	22 (15.0)	18 (12.2)
T4	3 (2.0)	18 (12.2)	5 (3.4)	4 (2.7)
N stage				
N0	19 (12.9)	8 (5.4)	0 (0)	0 (0)
N1	16 (10.9)	8 (5.4)	16 (10.9)	7 (4.8)
N2	16 (10.9)	8 (5.4)	27 (18.4)	15 (10.2)
N3	0 (0)	1 (0.7)	5 (3.4)	1 (0.7)
Clinical stage				
I	3 (2.0)	0 (0)	0 (0)	0 (0)
II	12 (8.2)	0 (0)	8 (5.4)	1 (0.7)
III	32 (21.8)	6 (4.0)	30 (20.5)	16 (10.9)
IVa	3 (2.0)	17 (11.6)	9 (6.1)	3 (2.0)
IVb	1 (0.7)	2 (1.4)	1 (0.7)	3 (2.0)

Table 3 Comparison of traditional Chinese medicine (TCM) syndrome types and imaging characterization in patients with nasopharyngeal carcinoma

TCM syndrome typing	Lung Heat type case (%)	Blood Stasis type case (%)	Phlegm Congealment type case (%)	Blood Stasis-Phlegm Congealment type case (%)	χ^2	<i>P</i>
Total cases	51 (34.7)	25 (17.0)	48 (32.7)	23 (15.6)		
Confined to nasopharynx					1.59	0.21
One side	7 (4.8)	0 (0)	6 (4.1)	0 (0)		
Bilateral	44 (29.9)	25 (17.0)	42 (28.6)	23 (15.6)		
Paranasopharyngeal space invasion					3.64	0.06
No	11 (7.5)	0 (0)	8 (5.4)	0 (0)		
Yes	40 (27.2)	25 (17.0)	40 (27.2)	23 (15.6)		
Neck lymph node metastasis					34.34	0.00
No	23 (15.6)	9 (6.1)	0 (5.4)	0 (0)		
Yes	28 (19.0)	16 (10.9)	48 (32.7)	23 (15.6)		
Invaded skull base					4.55	0.04
No	23 (15.6)	0 (0)	21 (14.3)	1 (0.7)		
Yes	28 (19.0)	25 (17.0)	27 (18.4)	22 (15)		

Relationship between TCM syndrome typing and radiosensitivity

There was no significant difference in radiosensitivity among syndrome types at the accumulated doses of 20 Gy, 40 Gy and 60 Gy ($\chi^2 = 0.226, 0.650$ and $0.319, P > 0.05$).

In contrast, radiosensitivity was significantly altered at 3 months post-therapy for different syndrome types ($\chi^2 = 22.99, P < 0.05$) with the radiosensitivity of Blood Stasis type and Blood Stasis-Phlegm Congealment type poorer than Lung Heat type and Phlegm Congealment type (Table 4).

Table 4 Comparison of TCM pattern types and radiosensitivity in patients with nasopharyngeal carcinoma

TCM typing	Lung Heat type case (%)	Blood Stasis type case (%)	Phlegm Congealment type case (%)	BloodStasis-Phlegm Congealment type case (%)	χ^2	P
Total cases	51(34.7)	25(17.0)	48(32.7)	23(15.6)		
20 Gy clinical evaluation	51(34.7)	25(17.0)	48(32.7)	23(15.6)	5.66	0.23
CR	0(0)	0(0)	3(2)	0(0)		
PR+	5(3.4)	1(0.7)	2(1.4)	2(1.4)		
PR	8(5.4)	4(2.7)	13(8.8)	7(4.8)		
PR-	19(12.9)	11(7.5)	13(8.8)	5(3.4)		
SD	19(12.9)	9(6.1)	17(11.6)	9(6.1)		
40 Gy clinical evaluation					2.47	0.65
CR	7(4.8)	1(0.7)	14(9.5)	3(2.0)		
PR+	14(9.5)	4(2.7)	11(7.5)	5(3.4)		
PR	20(13.6)	13(8.8)	10(6.8)	10(6.8)		
PR-	8(5.4)	7(4.8)	11(7.5)	5(3.4)		
SD	2(1.4)	0(0)	2(1.4)	0(0)		
60 Gy clinical evaluation					3.52	0.32
CR	20(13.6)	8(5.4)	25(17)	10(6.8)		
PR+	16(10.9)	11(7.5)	8(5.4)	5(3.4)		
PR	14(9.5)	5(3.4)	11(7.5)	7(4.8)		
PR-	1(0.7)	1(0.7)	4(2.7)	1(0.7)		
SD	0(0)	0(0)	0(0)	0(0)		
3 months post-treatment clinical evaluation					22.99	0.00
CR	39(26.5)	17(11.6)	39(26.5)	10(6.8)		
PR+	11(7.5)	6(4.1)	7(4.8)	6(4.1)		
PR	1(0.7)	2(1.4)	2(1.4)	6(4.1)		
PR-	0(0)	0(0)	0(0)	1(0.7)		
SD	0(0)	0(0)	0(0)	0(0)		

Discussion

In this study, we observed the following in syndrome typing in NPC patients: Lung Heat type accounted for the highest proportion of 34.7%, Phlegm Congealment type accounted for 32.7%, Blood Stasis type accounted for 17.0% and Blood Stasis-Phlegm Congealment type accounted for the lowest proportion of 15.6%. Phlegm Congealment and Blood Stasis-Phlegm Congealment types were more likely to suffer from lymph node metastasis, while Blood Stasis and Blood Stasis-Phlegm Congealment types had a greater risk of the destruction of bone in the skull base. Residual tumor tissue was greater in Blood Stasis and Blood Stasis-Phlegm Congealment types than in Lung Heat and Phlegm Congealment types. Radiosensitivity in Blood Stasis and Blood Stasis-Phlegm Congealment types was lower than Lung Heat and Phlegm Congealment types 3 months after radiotherapy.

NPC is called Phlegm-accumulation (*Tan-yong*) in TCM. The *Treatise on Pestilence* (*Wen Yi Lun*) states “if the disease generates without obvious exo-pathogenic factors, it must be caused by the residual of latent pathogenic

factors.” Characteristics of syndrome distribution correspond to disease development. At the condition of weak healthy-*qi* and disorder to *zang-fu* viscera, pathogenic factors invade the body and gather, leading to lung heat accumulation, or phlegm congealment (blood stasis). These pathogenic products block collaterals and meridians, massing to form the tumor. Thus, NPC is also termed “latent pathogenic factor” (*Fu-xie*) and “residual toxin” (*Yu-du*).

Studies on the relationship between TCM syndrome typing and imaging characterization are rare, with most studies focusing on the relationship between TCM syndrome typing and cervical lymph node enlargement^[18-20]. When collective lymphatic tissue is present in the nasopharynx with abundant lymphatic drainage, the incidence of nodal metastasis of NPC is rather high. In fact, it has been reported in 60%–90% of NPC patients who were preliminarily diagnosed with nodal metastasis, with neck mass accounting for 36%–45% of the first presentation of NPC and roughly 10% of neck mass presenting as the only symptom^[18,19]. For these reasons, previous studies have focused on the relationship between TCM syndrome typing and cervical lymph node enlargement.

In one such study, a correlation between TCM syndrome typing and cervical lymph node enlargement was observed ($P < 0.05$)^[20]. NPC patients were classified into Blood Stasis, Stagnant Fire and Turbid Phlegm types. Patients without cervical lymph node growth were predominantly typed as Blood Stasis or Stagnant Fire. In addition, when enlarged lymph node diameter measured less than 3 cm, there was an insignificant difference in the syndrome distribution of the three types. However, when enlarged lymph node diameter measured greater than 3 cm, Turbid Phlegm typing was more prevalent with a significant difference in the syndrome distribution of the three types ($P < 0.01$). Thus, the authors concluded the existence and size of enlarged lymph nodes are a reference index in TCM syndrome typing for NPC.

In another study, NPC patients were classified into five TCM syndrome types, including Lung Heat, Blood Stasis, Phlegm Congealment, Blood Stasis-Phlegm Congealment and Qi-blood Deficiency^[21]. The results demonstrated a consistent correlation between TCM syndrome typing and cervical node metastasis, with patients of Phlegm Congealment type commonly associated with cervical node metastasis, followed by patients typed with Blood Stasis-Phlegm Congealment. Pathogenic factor-phlegm was also presented as an important factor in the regional nodal metastasis of NPC. Thus, the TCM treatment could be prescribed in the angle of phlegm; by invigorating the spleen to dissolve, or remove the phlegm, the phlegm-dampened constitution of the NPC patients could be modified, improving the prognosis.

In our study, we demonstrated TCM syndrome typing had no association with the unilateral or bilateral location of tumor or the invasion of parapharyngeal space. In contrast, the destruction of bone in the skull base was significantly different among the syndrome types, as resolved by imaging. Blood Stasis and Blood Stasis-Phlegm Congealment types had a greater risk of destruction of bone in the skull base, whereas Blood Stasis-Phlegm congealment type was more prone to nodal metastasis and destruction of bone in the skull base. As NPC patients advanced to Blood Stasis-Phlegm Congealment typing, healthy-qi deficiency and a predominance of pathogenic factors was indicated. With the kidney essence exhausted and phlegm pertained to Yin pathogen, the qi and blood circulation would be blocked. The aforementioned might consume the qi and body fluid, aggravating blood stasis in the collaterals and meridians. As a result, the immune system would lose the supervision over the tumor, leading to damage of the lymphatic and blood vasculature. Thus, Blood Stasis-Phlegm Congealment typing occurred in the advanced stages of NPC.

It is widely accepted tumors isolated from different individuals express unique biological profiles. Consistent

with this, we observed variances in radiosensitivity for tumors of different pathologic types as well as for tumors of the same pathologic type^[22]. Years earlier, Hsieh *et al.*^[23] classified NPC as ascending, descending or mixed types according to the course of natural development, with descending or mixed types prone to metastasis. From prior long-term clinical studies of patients with NPC, we suggested four types of biological behavior: radio-sensitive with low metastasis-prone, radio-sensitive with high metastasis-prone, radio-resistant with low metastasis-prone and radio-resistant with high metastasis-prone^[9,24]. In an effort to further our understanding, we investigated the relationship between radiosensitivity and TCM syndrome typing. Our findings indicated an insignificant difference of radiosensitivity among syndrome types at the accumulated doses of 20 Gy, 40 Gy, and 60 Gy. However, radiosensitivity at 3 months after therapy significantly differed, with Blood Stasis and Blood Stasis-Phlegm Congealment types insensitive to radiation. In addition, radiosensitivity also depended on blood circulation. Blood Stasis typed patients were in a condition of *yin-yang* impairment with an unsmooth flow of *qi*-blood. If complicated with phlegm congealment, vessel blockage would be more severe and radioresistance would be intensified.

The practice of TCM is well founded in China, employing syndrome differentiation as a basis of treatment, aiming to clarify the nature of disease. Typing is also the premise of the treatment, including establishment of a therapeutic method, prescription and medication. Pathogenically, Lung Heat, Blood Stasis, Phlegm Congealment and Blood Stasis-Phlegm Congealment types are the progressive stages in the development of NPC. The lung is responsible for the dispersing and descending *qi* in the body, while lung-*yin* nourishes the whole body. Long-term accumulation of lung heat may scorch the body fluid into phlegm, possibly affecting *qi*-blood circulation, causing blood stasis in collaterals and meridians resulting in *qi* stagnation, greater phlegm retention and an inhibition of *qi* activity. In addition, *qi* stagnation furthers the generation of phlegm and results in long-term blood stasis. Both blood stasis and phlegm coagulation obstruct the *qi*-blood circulation. As observed in our study, Blood Stasis and Blood Stasis-Phlegm Congealment typed patients exhibited reduced radiosensitivity. It would be of great significance to increase radiosensitivity and improve the quality of life by improving blood circulation with the associated TCM treatment. To explore whether individualized TCM treatment for radiosensitive and radioresistant NPC patients is helpful, a 5-year overall survival rate would be a constructive topic for future study.

To conclude, medical imaging verified that Blood Stasis and Blood Stasis-Phlegm Congealment types were prone to

the destruction of bone in the skull base. Moreover, these two types showed a trend toward radioresistance in the short-term. Finally, Blood Stasis-Phlegm Congealment type was more likely to metastasize to the cervical nodes. Thus, our study has established a good foundation for the integration of traditional Chinese and modern medical methods for the treatment patients afflicted with NPC. However, an effort to determine a more accurate relationship between TCM syndrome typing and radiosensitivity should be conducted by a long-term, follow-up study.

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